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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/002,211	12/05/2001	Milton D. Goldenberg	IMMU:003US1	5605

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EXAMINER	
DAHLE, CHUN WU	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/002,211	GOLDENBERG, MILTON D.	
	Examiner	Art Unit	
	CHUN DAHLE	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *78-86 and 93-113* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *78-86 and 93-113* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission, filed on August 25, 2008, has been entered.

2. Applicant's amendment to the claims, filed August 25, 2008, has been entered.

Claims 109-113 have been added.

Claims 1-77 and 87-92 have been previously canceled.

Claims 78-86 and 93-113 are pending and currently under consideration as they read on the originally elected species of a method of treating immune thrombocytopenic purpura (ITP) and LL2 antibody.

3. This Office Action will be in response to applicant's arguments, filed on August 25, 2008.

The rejections of record can be found in the previous Office Action, mailed on August 17, 2006, March 9, 2007, and July 26, 2007, and April 23, 2008.

4. Upon further consideration, the prior rejection under 35 U.S.C. 112, second paragraph, has been withdrawn.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 78-86, 93-108, and newly added claims 109-113 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record.

Applicant's arguments, filed on August 25, 2008, have been fully considered but have not been found persuasive.

Applicant continues to assert that one of skill in the art would known that applicant is in possession of the genus of the claimed B-cell antibody. Applicant once again asserts that the common attribute for the species within the genus of the B-cell antibody is the ability to bind B cells. Applicant asserts that the disclosed single species of antibody, LL2 is sufficient to support the entire genus of B-cell antibody.

This is not found persuasive for following reasons:

Once again, the genus of the claimed B-cell antibody is extremely large. Once again, the instant specification discloses that antibodies can be made using antigens isolated from cell membrane as well as intracellular proteins (e.g. see lines 5-12 on page 11 of the instant specification). Thus, the claimed genus of B-cell antibody is not limited to those that bind B-cell surface proteins such as CD20; rather, B-cell antibody includes any antibody that binds proteins on surface of B-cells as well as those intracellular proteins. Thus, the claimed genus of B-cell antibody is not limited to those that bind B-cell surface proteins such as CD20; rather, B-cell antibody includes any antibody that binds proteins on surface of B-cells as well as those intracellular proteins. As discussed in prior Office Action, it was known in the art at the time of the invention that a mammalian cell may contain up to 30,000 different mRNA sequences that can be translated to proteins as evidenced by the teachings of Sees et al. (EP 0739980, see page 3 in particular). Further as discussed in the previous Office Action mailed on August 17, 2006, Youinou et al. (Autoimmunity Reviews 2006 5:215-221, reference on PTO-892 mailed on

August 17, 2006) B-cells express a variety of different cell surface markers depending on the B-cell subsets and locations (e.g. see Table 1 on page 217). Therefore, the genus of the claimed B-cell antibody can contain up to 30,000 different antibodies. Applicant has not provided sufficient evidence to show that there is a known or disclosed correlation or the sufficiently detailed relevant identifying characteristics of the large genus of the claimed "B-cell antibody or fragment thereof". Applicant has not addressed the teachings of Seed et al. and Youinou et al. in her Remarks. The specification does not describe any structural features of the potential 30,000 B cell proteins as well as antibodies to those proteins that would shared by the single species LL2 antibody and its antigen.

In contrast to applicant's, it is noted that the fact that antibodies bind B cell surface antigen is not considered relevant identifying characteristics that couple with a known or disclosed correlation between function and structure of the broadly diverse antibodies (e.g. antigen specificity) employed in the claimed methods. Even if all of the genus of B-cell antibody can be made, not all of the B-cell antibodies can be used in the claimed method of treating an immune disease. It is not clear that which of the monoclonal antibodies that react with human B lymphocytes taught in Table 1 of Kenneth et al. can be used to treat immune disease.

Given that there exist a large amount of B cell proteins that can be used to make B-cell antibodies, the structure of the species within the claimed genus would be expected to vary unpredictably from the structure of the single, described LL2 antibody. The disclosed method of ablating normal cells in a subject by administering LL2 antibody is not a "representative number" of species within the claimed method encompassing administering B cell antibody. Accordingly, the specification does not provide a representative number of species or sufficient common structural features to show that applicant would have been in possession of the claimed genus as a whole at the time of the filing.

7. Claims 93, 97-100, and newly added claim 107 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record.

The claims recite "a B-cell antibody or fragment thereof ..... wherein the antibody or fragment thereof is a polyclonal, chimeric or hybrid antibody which binds multiple epitopes or antigens" as part of the invention.

Given that there is insufficient written description in the specification as-filed regarding "B-cell antibody" for reasons discussed above, applicant is not in possession of any B-cell antibody that has additional antigen specificity (e.g. chimeric or hybrid) for reasons set forth in the previous Office Action mailed on July 26, 2007.

Once again, given the absence of additional rebuttal to the outstanding rejection of record in applicant's Remarks, filed on December 26, 2007, the rejection has been maintained for reasons of record.

8. Claims 102 and 105 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record.

The term "B-cell immune disease" recited in claims 102 and 105 is not supported by the original disclosure or claim as filed.

Applicant's arguments, filed on August 25, 2008, have been fully considered but have not been found persuasive for following reasons:

Applicant argues that the Examiner suggested that applicant amend the claims to "recite particular characteristics of the immune disease". Applicant argues that page 12 of the instant specification discloses LL2 targets B cells and is useful in treating immune disease. Thus,

applicant asserts that the phrase "B-cell immune disease" is not new matter.

This is not found persuasive for following reasons:

In contrast to applicant's assertion, it is noted that the there is no record showing that the Examiner suggested the phrase "B-cell immune disease". In addition, the amendment to the claims must not introduce new matter. Here, the specification does not provide sufficient support for a method of treating "B-cell immune disease" by administering a B-cell antibody. The specification only disclose "immune disease". The instant claims now recite "B-cell immune disease" which is not clearly disclosed in the specification. Therefore, the claims represent a departure from the specification and claims originally filed. Applicant's reliance on generic disclosure (an immune disease) do not provide sufficient direction and guidance to the features currently claimed.

Therefore, applicant's arguments have not been found persuasive.

9. Claims 78-86, 93-108 and newly added and newly added claims 109-113are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record.

Applicant's arguments, filed on August 25, 2008, have been fully considered but have not been found persuasive.

Applicant argues that Lym-1 and Lym-2 antibodies taught by Meyer are not B-cell antibodies, but are HLA-DR antibodies that bind only at low levels of normal B cells. Applicant asserts that one of skill in the art would not select Lym-1 and Lym-2 for the claimed methods.

This is not found persuasive for following reasons:

In contrast to applicant's assertion, it is once again noted that the claimed method encompasses the administering B-cell antibody to ablating normal cells in a subject. Applicant repeatedly asserts that the B-cell antibody" is defined as any antibody that binds B cell surface proteins as well as intracellular proteins. Applicant appears to be inconsistent with respect to the claimed "B-cell antibody". Is HLA-DR not expressed on B cells, malignant or normal? Applicant has not show any objective evidence indicating HLA-DR is expressed on B cells. Thus, based upon applicant's own assertion and definition regarding B-cell antibody, one of skill in the art would consider anti-HLA-DR antibody to be "B-cell antibody" but would not be enabled to administer such antibody to ablate normal cells in a subject. Given that the instant claims recite any B-cell antibody or fragment thereof without considering the level of antigens that is expressed on normal B cells; one of skill in the art would not be able to make and use the claimed methods.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 78, 81-86, 102-105, and newly added claims 109-113 are rejected under 35 U.S.C. 102(b) as being anticipated by Meyer et al. (US Patent 4,861,579) for reasons of record.

Meyer et al. teach a method of treating immune diseases such as infection, autoimmune disease by administering an anti-B antibody or fragment thereof (see entire document, particularly columns 1-3). Meyer et al. further teach that said antibody can be conjugated with therapeutic agents such as radioisotopes, toxins, cytotoxic agents (e.g. see column 2).

Applicant's arguments, filed on August 25, 2008, have been fully considered but have not been found persuasive.

Applicant argues that the claims have been amended to recite "a method of ablating normal cells in a subject…". Applicant argues that Meyer et al. do not teach anti-B cell antibody ablating normal cells. Thus, applicant asserts that Meyer et al. do not anticipate the claims.

This is not found persuasive for following reasons:

In contrast to applicant's reliance on the preamble of the claims, it is noted that the claimed language or limitation does not appear to result in a manipulative difference in the method steps when compared to the prior art disclosure. Given that Myer et al. recognize that antibodies to malignant B-lymphocytes are often cross-reactive with normal B-lymphocytes, the prior art method of administering the same B-cell antibody would inherently result in ablating normal cells including spleen cells in a subject. It is reasonable to conclude that eh same patient is being administered the same active agent of B-cell antibody by the same mode of administration in both the instant claims and the prior art reference. The fact that applicant may have discovered another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 00-1304 (CAFC 4/20/01).

Therefore, applicant's arguments have not been found persuasive.

12. Claims 78, 79, 81, 93, 102-107, and newly added claims 109-113 are rejected under 35 U.S.C. 102(b) as being anticipated by Bussel et al. (Blood 1988 72;1:121-127) as evidenced by de Grandmont et al. (Blood 2003 101;8:3065-3073) for reasons of record.

As stated previously, *"Bussel et al. teach method of treating immune thrombocytopenic purpura by administering intravenous immunoglobulins (IVIG) (see entire document, particularly Material and Methods on pages 121 and 124).*

As evidenced by de Grandmont et al, IVIGs are IgG solutions prepared from pooled plasma of healthy human donors and contain antibodies reacting against a large repertoire of antigens, including those on B

lymphocytes (see entire document, particularly page 3065). Therefore, the reference method using IVIG would inherently encompass intact B-cell antibodies.

Further, although the reference is silent about B-cell antibody, it does not mean that the referenced IVIG does not bind epitopes on B-cell. Since the Office does not have a laboratory to test the referenced IVIG, it is applicant's burden to show that the referenced IVIG does not contain B-cell antibodies. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980). Furthermore, it does not appear that the claim limitation results in a manipulative difference in the methods steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d1508 (CAFC2001). It is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable."

Applicant's arguments have been fully considered but have not been found persuasive.

Applicant argues that the prior art method of treating by administering IVIG does not involve ablating normal cells in a subject. Applicant repeats the argument that therapeutically active ingredient in IVIG is dimers interacting with Fc gamma receptors, not B-cell antibodies. Furthermore, applicant asserts that even if IVIG contains B-cell antibodies, the amount is not sufficient to meet the claimed "therapeutically effective amount" of B-cell antibody. Thus, applicant argues the reference teachings do not anticipate the claimed invention.

This is not found persuasive for following reasons:

It is noted that during patent examination, the pending claims must be "given their broadest reasonable interpretation consistent with the specification.". See MPEP 2111. Here, given that the instant specification discloses that antibodies can be made using antigens isolated from cell membrane as well as intracellular proteins (e.g. see lines 5-12 on page 11 of the instant specification), the claimed B-cell antibody includes any antibody that binds proteins on surface of B-cells. Therefore, IVIG that binds B cells are considered B-cell antibody.

Once again, in contrast to applicant's reliance on the mechanism of action of IVIG, it is noted that the mechanism of action disclosed by the prior art does not preclude that the methods and compositions of the prior art IVIG inherently would have had the properties of B-cell antibody recited in the claims because compositions comprising the same type of B-cell antibodies are administered to the same patients to treat the same type of autoimmune disease ITP to achieve the same result. Additionally, given that Grandmont et al. teach IVIG binds CD40 that is expressed on B-cell, IVIG would be considered to have B-cell antibody. Given that no clear definition was given regarding the broadly claimed B-cell antibody as well as applicant's assertion that B-cell antibody meant antibodies targeting B cell antigens (see Interview summary mailed on December 6, 2007), IVIG containing antibodies that bind CD40 expressed on mature B cells is considered B-cell antibody. Further, regarding applicant's arguments of "therapeutically effective amount", it is noted that the term is not defined in the instant specification. Thus, the prior art method of treating ITP with the amount of IVIG to relief the symptoms is considered "therapeutically effective amount".

Therefore, applicant's arguments have not been found persuasive.

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. Claims 78, 80, 93, 95-101, 107, and 108 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meyer et al. (US Patent 4,861,579) in view of Sivam et al. (US Patent 5,116,944) for reasons of record.

As has been discussed previously, the teachings of Meyer et al. have been discussed, supra. The reference teachings differ from the claimed invention by not describing Fv, , single

chain antibody, Fab, Fab', $F(ab')_2$, chimeric antibody, and antibody that is conjugated to cytokine.

Given the absence of additional rebuttal to the outstanding rejections of record in applicant's amendment, filed on August 25, 2008; the rejections are maintained for the reasons of record.

19. Claims 78 and 94 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meyer et al. (US Patent 4,861,579) in view of Fishwild et al. (Nature Biotech. 1996, 14:845-851) for reasons of record.

The rejection is in regard to the limitation of "human antibody".

Given the absence of additional rebuttal to the outstanding rejections of record in applicant's amendment, filed on August 25, 2008; the rejections are maintained for the reasons of record.

20. No claim is allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chun Dahle whose telephone number is 571-272-8142. The examiner can normally be reached on 8:30-5:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Eileen O'Hara can be reached 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Chun Dahle/
Primary Examiner, Art Unit 1644